CEMMA

universität ulm

NEWSLETTER No 4 January 2022

Dear CEMMA members,

Right in time for the beginning of the year 2022, we are back with a new issue of our CEMMA Newsletter.

Although Corona can be described as a bulky brake block, the members of our graduate program CEMMA were very productive also in the last year.
They continued to work very intensively on their dissertations, successfully submitted publications, participated in workshops and EMBO lectures. There were also some PhDs to celebrate, of course in compliance with the corona rules.
CEMMA will end in 2022 after achieving the DFG's maximum funding period for GRKs of 9 years.

The good news: The DFG is founding a new CRC "Aging at Interfaces" in Ulm . Congratulations!

About final activities for the RTG 1789, CEMMA, we will keep you informed.

We wish you an enjoyable and informative read.

-- Sabine Wörndle

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CEMMA welcomes new PhDstudents

Bryan Castano
He is working in the Research Group of Prof. Lisa Wiesmüller

Gauthami Armanath
She is working in the Research Group of Prof.. Birgit Liss

We cordially welcome the new RTG-PhDs and wish them a lot of success for their project!

More details on their projects will be available on the CEMMA homepage in the near future.

The Research Training Group (RTG) 1789 “Cellular and molecular mechanisms of ageing” (CEMMA) is funded by the German Science Foundation (DFG) July 2013 to June 2022.

Gratuated PhD students and date of defense

Congratulations to our PhD students

Aynur Sönmez
23. April 2020

Mona Vogel
25. February 2021

Smitha Srinivasachar
7. April 2021

Amanda Amoah
6. May 2021

Divisha Bhatia
30. September 2021

David Bayer
5. October 2021

We congratulate the graduated PhDs
and wish them all the best
and much success for their future!

GRK 1789 related first authorship publications

Disruption of orbitofrontal-hypothalamic projections in a murine ALS model and in human patients

David Bayer, Stefano Antonucci, Hans-Peter Müller, Rami Saad, Albert C. Ludolph, Jan Kassubek & Francesco Roselli

Translational Neurodegeneration 2021 May 31;10(1):17.
Full text: https://doi.org/10.1186

Abstract

Background: Increased catabolism has recently been recognized as a clinical manifestation of amyotrophic lateral sclerosis (ALS). The hypothalamic systems have been shown to be involved in the metabolic dysfunction in ALS, but the exact extent of hypothalamic circuit alterations in ALS is yet to be determined. Here we explored the integrity of large-scale cortico-hypothalamic circuits involved in energy homeostasis in murine models and in ALS patients.

Methods: The rAAV2-based large-scale projection mapping and image analysis pipeline based on Wholebrain and Ilastik software suites were used to identify and quantify projections from the forebrain to the lateral hypothalamus in the SOD1(G93A) ALS mouse model (hypermetabolic) and the $Fus^{\Delta NLS}$ ALS mouse model (normo-metabolic). 3 T diffusion tensor imaging (DTI)-magnetic resonance imaging (MRI) was performed on 83 ALS and 65 control cases to investigate cortical projections to the lateral hypothalamus (LHA) in ALS.

Results: Symptomatic SOD1(G93A) mice displayed an expansion of projections from agranular insula, ventrolateral orbitofrontal and secondary motor cortex to the LHA. These findings were reproduced in an independent cohort by using a different analytic approach. In contrast, in the $Fus^{\Delta NLS}$ ALS mouse model hypothalamic inputs from insula and orbitofrontal cortex were maintained while the projections from motor cortex were lost. The DTI-MRI data confirmed the disruption of the orbitofrontal-hypothalamic tract in ALS patients.

Conclusion: This study provides converging murine and human data demonstrating the selective structural disruption of hypothalamic inputs in ALS as a promising factor contributing to the origin of the hypermetabolic phenotype.

GRK 1789 related first authorship publications

T-cell dysregulation is associated with disease severity in Parkinson's Disease

Divisha Bhatia, Veselin Grozdanov, Wolfgang P Ruf, Jan Kassubek, Albert C Ludolph, Jochen H Weishaupt, Karin M Danzer
Journal Neuroinflammation, volume 18, Article number: 250 (2021)

Full text: https://doi.org/10.1186/s12974-021-02296-8

Abstract
The dysregulation of peripheral immunity in Parkinson's Disease (PD) includes changes in both the relative numbers and gene expression of T cells. The presence of peripheral T-cell abnormalities in PD is well-documented, but less is known about their association to clinical parameters, such as age, age of onset, progression rate or severity of the disease. We took a detailed look at T-cell numbers, gene expression and activation in cross-sectional cohorts of PD patients and age-matched healthy controls by means of flow cytometry and NanoString gene expression assay. We show that the well-pronounced decrease in relative T-cell numbers in PD blood is mostly driven by a decrease of $CD8^+$ cytotoxic T cells and is primarily associated with the severity of the disease. In addition, we demonstrate that the expression of inflammatory genes in T cells from PD patients is also associated with disease severity. PD T cells presented with increased activation upon stimulation with phytohemagglutinin that also correlated with disease severity. In summary, our data suggest that the consequences of disease severity account for the changes in PD T cells, rather than age, age of onset, duration or the disease progression rate.

GRK 1789 related first authorship publications

Nucleolar TFIIE plays a role in ribosomal biogenesis and performance

Tamara Phan, Pallab Maity, Christina Ludwig, Lisa Streit, Jens Michaelis, Miltiadis Tsesmelis, Karin Scharffetter-Kochanek, Sebastian Iben

Nucleic Acids Research, Volume 49, Issue 19, 8 November 2021, Pages 11197–11210
Full text: https://doi.org/10.1093/nar/gkab866

Abstract
Ribosome biogenesis is a highly energy-demanding process in eukaryotes which requires the concerted action of all three RNA polymerases. In RNA polymerase II transcription, the general transcription factor TFIIH is recruited by TFIIE to the initiation site of protein-coding genes. Distinct mutations in TFIIH and TFIIE give rise to the degenerative disorder trichothiodystrophy (TTD). Here, we uncovered an unexpected role of TFIIE in ribosomal RNA synthesis by RNA polymerase I. With high resolution microscopy we detected TFIIE in the nucleolus where TFIIE binds to actively transcribed rDNA. Mutations in TFIIE affects gene-occupancy of RNA polymerase I, rRNA maturation, ribosomal assembly and performance. In consequence, the elevated translational error rate with imbalanced protein synthesis and turnover results in an increase in heat-sensitive proteins. Collectively, mutations in TFIIE-due to impaired ribosomal biogenesis and translational accuracy-lead to a loss of protein homeostasis (proteostasis) which can partly explain the clinical phenotype in TTD.

GRK 1789 related first authorship publications

Nucleolar stress controls mutant Huntington toxicity and monitors Huntington's disease progression

Aynur Sönmez, Rasem Mustafa, Salome T Ryll, Francesca Tuorto, Ludivine Wacheul, Donatello Ponti, Christian Litke, Tanja Hering, Kerstin Kojer, Jenniver Koch, Claudia Pitzer, Joachim Kirsch, Andreas Neueder, Grzegorz Kreiner, Denis L J Lafontaine, Michael Orth, Birgit Liss, Rosanna Parlato

Cell Death & Disease 2021 Dec 8;12(12):1139
Full text: https://doi.org/10.1038/s41419-021-04432-x

Abstract
Transcriptional and cellular-stress surveillance deficits are hallmarks of Huntington's disease (HD), a fatal autosomal-dominant neurodegenerative disorder caused by a pathological expansion of CAG repeats in the Huntingtin (HTT) gene. The nucleolus, a dynamic nuclear biomolecular condensate and the site of ribosomal RNA (rRNA) transcription, is implicated in the cellular stress response and in protein quality control. While the exact pathomechanisms of HD are still unclear, the impact of nucleolar dysfunction on HD pathophysiology in vivo remains elusive. Here we identified aberrant maturation of rRNA and decreased translational rate in association with human mutant Huntingtin (mHTT) expression. The protein nucleophosmin 1 (NPM1), important for nucleolar integrity and rRNA maturation, loses its prominent nucleolar localization. Genetic disruption of nucleolar integrity in vulnerable striatal neurons of the R6/2 HD mouse model decreases the distribution of mHTT in a disperse state in the nucleus, exacerbating motor deficits. We confirmed NPM1 delocalization in the gradually progressing zQ175 knock-in HD mouse model: in the striatum at a presymptomatic stage and in the skeletal muscle at an early symptomatic stage. In Huntington's patient skeletal muscle biopsies, we found a selective redistribution of NPM1, similar to that in the zQ175 model. Taken together, our study demonstrates that nucleolar integrity regulates the formation of mHTT inclusions in vivo, and identifies NPM1 as a novel, readily detectable peripheral histopathological marker of HD progression.

GRK 1789 related review article

Septins in Stem Cells

Tanja Schuster, Hartmut Geiger

Front. Cell Dev. Biol., 09 December 2021
Full text: https://doi.org/10.3389/fcell.2021.801507

Abstract
Septins were first described in yeast. Due to extensive research in non-yeast cells, Septins are now recognized across all species as important players in the regulation of the cytoskeleton, in the establishment of polarity, for migration, vesicular trafficking and scaffolding. Stem cells are primarily quiescent cells, and this actively maintained quiescent state is critical for proper stem cell function. Equally important though, stem cells undergo symmetric or asymmetric division, which is likely linked to the level of symmetry found in the mother stem cell. Due to the ability to organize barriers and be able to break symmetry in cells, Septins are thought to have a significant impact on organizing quiescence as well as the mode (symmetric vs asymmetric) of stem cell division to affect self-renewal versus differentiation. Mechanisms of regulating mammalian quiescence and symmetry breaking by Septins are though still somewhat elusive. Within this overview article, we summarize current knowledge on the role of Septins in stem cells ranging from yeast to mice especially with respect to quiescence and asymmetric division, with a special focus on hematopoietic stem cells.

Lecture Series: Talk and Roundtable

7th September 2021, in person:

Helen Tauc, PhD, Genentech, Immunology Discovery, South San Francisco, USA:

Helen Tauc is an alumna of Ulm University MolMed and is working as PostDoc in the industry. In the roundtable session after the talk the CEMMA-PhDs had the opportunity to get interesting insights into post-PhD career opportunities from her perspective .

“Identity Crisis? Exploring lineage (in)fidelity in the aging intestine”

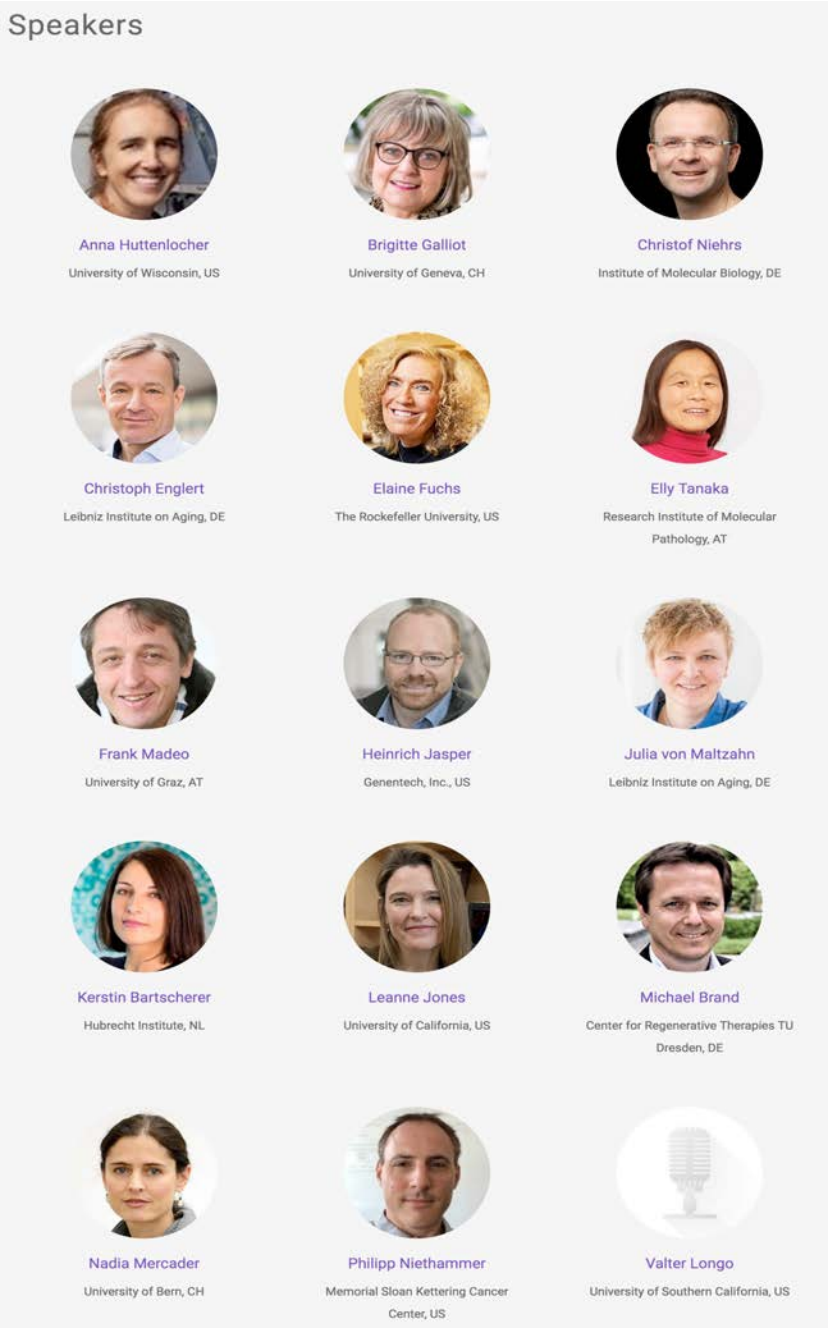
The intestine is a multifunctional organ, serving not only as the main route of nutritional intake but also as the site of immune-microbial interactions where host defense mechanisms keep pathogenic threats at bay. Intestinal integrity relies on the appropriate number and function of diverse intestinal epithelial cell types, all of which are maintained and regenerated by resident intestinal stem cells (ISCs). During aging, changes in cell composition and a decline in stem cell function and regenerative capacity have been reported, but the mechanisms underlying these changes are poorly understood, especially in mammals. My research investigates these changes by using both the fruit fly, Drosophila melanogaster, and mouse model systems. In particular, I focus on understanding how aging impacts cell composition and mechanisms controlling lineage fate decisions. In flies, using single cell, transcriptomic and epigenomic methods, I found that old ISCs exhibit changes in their transcriptome that bias them toward the secretory lineage, resulting in an over-production of enteroendocrine (EE) cell progenitors and mature EE cells. These changes are caused by imbalanced Polycomb and trithorax function, and my studies suggest that inflammatory and stress signaling (caused in part by bacterial dysbiosis) contributes to the bias towards the secretory lineage. In preliminary work in the mouse intestine, I have explored the evolutionary conservation of the age-related changes observed in flies. Single cell RNA-seq showed significant age-related changes in the secretory fate lineage of the mouse small intestine, suggesting a conserved effect of aging on maintaining appropriate cell fate dynamics. The underlying mechanisms of age-related lineage infidelity, and how cell fate changes impact organismal health- and lifespan, are currently under further investigation. I believe that these studies will provide critical insights into stem cell aging and associated age-related diseases.

Lecture Series

6th to 10th September 2021 virtual
The RTG CEMMA offered the opportunity to participate in the

EMBO/FEBS Lecture Course:

Molecular mechanisms of aging and regeneration: From Hydra to humans.



Workshop: CareerMaker – Coaching, online

The CarrerMaker workshop took place online between May 27th and early July. It was recommended for doctoral students in the late stages of their careers. The course was fully booked with 8 participants from the CEMMA group.

CareerMaker

A blended learning course.
Building and pursuing your personal career vision with special focus on gender-related questions.

During your academic studies and PhD work, you spend plenty of time learning scientific facts and methods in your specific field of study. But no one teaches you how to translate that academic knowledge into a successful career that matches your goals and talents. This course introduces you to a systematic approach for building a personal career vision, based on your individual goals, experiences and talents – be it in an academic setting or beyond. You'll be enabled to put yourself into the driver's seat of your career and efficiently tackle typical obstacles along the way. Specific questions, hurdles or uncertainties connected to gender roles will be discussed.

Module 1: Kickoff Workshop
Group work, two half days:

- Finding out about your knowledges, skills, talents and wishes
- Defining your sweet spot in the multidimensional career universe
- Specifics of academic career pathways
- The formal and informal job market
- Your next steps / goals

Module 2: Online Self-Study Period
One month, individual work, with additional input, nudges and exercises on:

- Your progress along your next steps / goals
- Tools and tips for career support, decision making and from Positive Psychology

Module 3: One-on-one Career Coaching
Individual work with the instructor, up to 1,5 hrs, covering:

- A deep dive into your specific questions
- Refining your personal career vision
- Addressing concrete challenges and developing individual plans for action

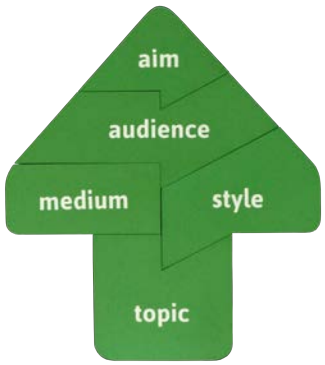
Your Course Instructor
Dr. Simone Cardoso de Oliveira is a professional career coach. Trained as a neuroscientist, she has many years of professional experience in diverse professional fields, ranging from research to management, from university to private companies, from development to sales, and from public employee to free-lancer. Career pathways and perspectives of academics have always been a matter of heart to her.

Feedback from participants:
"It was a pleasure to work with Simone. It was a great workshop with new good ideas and hints and it is really high recommended. Also the time for your self-coaching is very important and good so that you can reflect yourself and see what you have to do to change or edit to be successful."

Workshop: Basics of Science Communication

Since the impact of science communication has steadily increased in recent years, CEMMA organised a workshop on science communication to raise awareness of this issue among PhDs.
The seminar was held by Dr. Tobias Maier and Dr. Holger Breithaupt from the National Institute for Science Communication in Karlsruhe (NaWiK) in a virtual, interactive format on November 18. - 19. 2021.
11 PhD students participated, 8 of them from the CEMMA group.
Feedback from participants: "This seminar was held at a time when most scientists need something like this, as most of us are struggling with the lack of confidence in science."

The key elements of successful science communication are illustrated in the NaWiK arrow: focused topic, defined aim, directed to specific audience, adapted mediumof choice and appropriate style



Basics of Science Communication

Time*	Contents#
09:00	Setting the frame of the seminar
09:30	The main actors and changes in the science communication landscape
10:30	Coffee break
10:50	Getting your message across clearly with your own core message
11:30	The NaWik Arrow as a framework for successful science communication
12:30	Introduction home exercise and end of day 1
09:00	Analysis home exercise on communication strategy
10:00	The factors underlying trust in science – and in scientists
10:30	Coffee break
10:50	Target audiences and appropriate communication style
11:30	Dealing with the media and open questions
12:30	Evaluation and end of day 2

Scientific Retreat

After a time of online-only it was a special delight to organize the CEMMA-Retreat on Friday, December 10th in person under university corona rules.
The opening speech fed the participants' discussion spirit and everyone was enjoying to meet the colleagues in person again.
The PhD students gave excellent presentations on their projects, covering the wide range of the thematic spectrum of the aging research in CEMMA. The scientific methods and results were discussed with all participating supervisors and PhDs.

CEMMA - Retreat 2021

Friday 10th December 2021 in person, N27 Multimedia-Room

10:00 – 10:10	Hartmut Geiger	Welcome Introduction
10:10–10:30	Verena Bopp AG Danzer	The role of aging and alpha-synuclein oligomer load on Parkinson's Disease pathogenesis
10:30 – 10:50	Konstantinos Tsesmelis AG Wirth	Impact of astroglial redox imbalance on CNS homeostasis and aging.
10:50 – 11:10	Sruthi Krishnamurty AG Roselli	Hypothalamic neuropeptides regulating metabolism in ageing and neurodegeneration
11:10 – 11:30	Nicole Wiederspohn AG Liss	Interplay between α-synuclein and metabolic stress in neurons differently affected during Parkinson's disease
11:30 – 11:50	Philipp Haas AG Scharffetter-Kochanek	The Adaptive Response of Old ABCB5^{+} MSCs is Changed Upon Exposure to LPS
11:50 – 12:40	**BREAK**	"LUNCHPAKET-Surprise"
12:40 – 13:00	Tanja Schuster AG Geiger	Polarity Quantification
13:00 – 13:20	Habib Rahimi AG Buske	Age-related changes in the human HSC methylome affect gene regulatory regions critical to HSC function
13.20 – 13:40	Heike Schreier AG Wiesmüller	Mechanisms of mitochondrial DNA maintenance-impact on aging
13:40 – 14:00	Dominik Pflumm AG Schirmbeck	SARS-CoV-2 vaccine design to characterize the humoral response in young and old C57BL/6 mice
14:00 – 14:10	Hartmut Geiger	VERABSCHIEDUNG

Scientific Retreat 2021

Some impressions

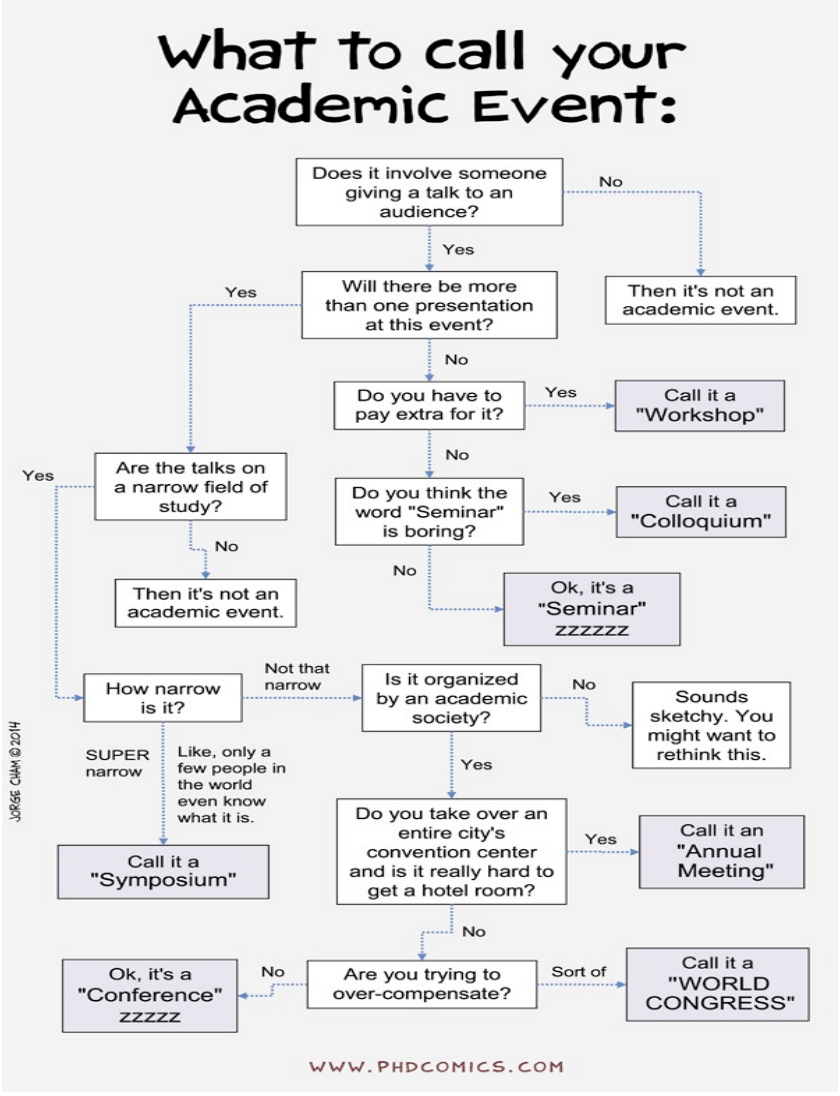
We are all looking forward to the next meeting, keeping fingers crossed that it will be in person again.

Online – Info´s

Finally for you to be informed:
In March 2021, the DFG established ten "Principles of Effective Career Support in Science" to provide effective support to scientists in early career phases .

The recommendations are helping to ensure that appropriate measures and structures for supporting early career investigators become the norm.
https://www.dfg.de/download/pdf/foerderung/wissenschaftliche_karriere/prinzipien_karriereunterstuetzung.pdf

Last but not least some Science fun:
(www.phdcomics.com)



The END